IBUPROFEN-CONTAINING SOFT GELATIN CAPSULES

Technical Field of the Invention

The technical field of the invention relates to ibuprofen-containing soft gelatin capsules, pharmaceutical compositions of a substantially clear ibuprofen solution, and process for their manufacture. It also relates to pharmaceutical compositions of substantially clear solutions containing ibuprofen and pseudoephedrine and use of said compositions for treatment of common cold and flu-like symptoms.

Background of the Invention

Common cold and flu-like illnesses are endemic, with a peak incidence during the winter months and a reported frequency of two to eight episodes per person per year. Exemplary formulations for treatment of cough, cold, cold-like, allergy, sinus and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith generally contain an analgesic (aspirin or acetaminophen) and one or more antihistaminics, decongestants, cough suppressants, antitussives and expectorants.

The use of non-steroidal anti-inflammatory drugs to combat inflammation and attendant pain is accepted in medical practice. Among the most commonly used drugs of the non-narcotic analgesic class of drugs are aspirin, acetaminophen, ibuprofen, ketoprofen, diclofenac and naproxen and their salts (e.g., lysine, arginine, sodium and potassium). Aspirin, acetaminophen and ibuprofen have heretofore been included as the pain reliever and fever-reducing component in conventional cough/cold multisymptom alleviating compositions. These commercially marketed products generally contain in addition to aspirin, acetaminophen or ibuprofen, one or more antihistaminics, decongestants, cough-suppressants, antitussives and expectorants. The combination of ibuprofen and a decongestant (pseudoephedrine hydrochloride) is commercially available as capsule, suspension and tablet dosage forms.

Ibuprofen is a white powder which is practically insoluble in water. It is absorbed from the gastro-intestinal tract and the peak plasma concentrations occur approximately one to two hours after ingestion of the solid powder or crystal form.

A standard dosage form widely in use for the delivery of ibuprofen is the solid dosage form or tablet. The absorption time of a solid dosage form (tablet) is relatively

long because of two significant factors. The first factor is that the drug; being introduced as a solid, needs to first dissolve before the body can absorb it. The second factor is that absorption into the body is further delayed because ibuprofen is practically insoluble in water or the acidic environment of the stomach.

Soft gelatin capsules are a unique drug delivery system that can provide distinct advantages over traditional dosage forms such as tablets, hard-shell capsules, and liquids. Some of the major advantages of softgels include improved bioavailability (increased drug absorption, speed of product development, enhanced drug stability (protection against oxidation, photodegradation, and hydrolysis in lipophilic systems), superior patient compliance/consumer preference (ease of swallowing, appealing appearance, absence of objectionable taste, and convenience) and pharmaceutical elegance, excellent dose uniformity, better tamper evidence (tampering leads to puncturing and visible leakage) and safer handling of highly potent or cytotoxic drug compounds. Soft gelatin capsules filled with clear or transparent liquids are generally preferred due to their aesthetic appeal.

However, despite these advantages of liquid compositions, it is not always possible to prepare a clear, liquid composition of poorly soluble actives such as ibuprofen, to be filled into soft gelatin capsules. Also, the choice of solvents available for use in liquid compositions is limited by safety, compatibility, stability, and economic concerns. Furthermore, the use of large volumes of solvents for solubilizing pharmaceutical actives is undesirable because the resulting solutions would be so dilute as to require impractically large dosages for delivering a therapeutically effective amount of the active ingredient. In such situations, it would be difficult, if not impossible, to encapsulate such large volumes into only one or two gelatin capsules and yet have them be of a reasonable size for easy swallowing. The formulation becomes more complicated when more than one active are to be incorporated.

One approach to overcoming these solubility problems has been to incorporate co-solvents and surfactants into the compositions, although it may not be possible in all cases to incorporate co-solvents or surfactants into a pharmaceutical composition. Several processes have been developed in efforts to increase the solubility and, hence, the bioavailability of ibuprofen.

U.S. Patent No. 5,071,643 discloses a solvent system that is characterized as enhancing the solubility of pharmaceuticals for encapsulation. The system involves the use of gelling agents such as sodium stearate, sodium palmitate and calcium acetate to improve solubility of pharmaceutical ingredients into polyethylene glycol.

U.S. Patent No. 6,387,400 discloses a process for improving concentration of a pharmaceutically active ingredient relative to fill composition. The process includes a two step process. In step one, a suspension of part of a drug is made in polyethylene glycol with a molecular weight of 200 daltons to 100,000 daltons and solubilizing it subsequently with hydroxide ion. In step two, the remaining drug is added and the resulting suspension is solubilized by adding the remaining part of hydroxide ion. The ratio of drug to fill material by weight is 1:2 and/or 5:9.

U.S. Patent No. 5,376,688 discloses the preparation of pharmaceutically accepted solution of acidic, basic and amphoteric pharmaceutical agent suitable for encapsulation in gelatin capsule for subsequent oral administration and includes pharmaceutical agent, an ion species and solvent system. The invention uses hydroxide or hydrogen ion species to carry out the ionization of the acidic pharmaceutical agent and the solvent system utilized consists essentially of one or more of diethylene glycol monoethylether, glycerol caprylate, polyglycerol oleate or mixtures thereof.

WO 02/069936 discloses the solubilization of ibuprofen using diethylene glycol monoethylether, caprylocaproyl macrogols-8 glycerides or mixtures as the solvent and alkali metal bicarbonate for the partial ionization of ibuprofen and subsequent conversion into alkali metal salt.

Thus, the problem of finding an appropriate solvent system for a soft gelatin capsule fill still exists for ibuprofen. It has been difficult to achieve a soft gelatin capsule of small enough size to be acceptable to patients, i.e., small enough to swallow while still including in that capsule a sufficient amount of ibuprofen in a clear and stable solution to provide an effective unit dose.

In the present invention, the inventors have prepared substantially clear solutions of ibuprofen as well as ibuprofen in combination with pseudoephedrine by utilizing the solubilizing properties of polyethylene glycol and ionizing properties of metal carbonates

for the partial or complete conversion of ibuprofen into its metal salts. Metal carbonates facilitate the conversion of ibuprofen to ibuprofen salt with the help of the evolved carbon dioxide in the above reaction. The addition of suitable surfactants aid in dissolution and/or dispersion of ibuprofen after it is released from the dosage form.

Summary of the Invention

In one general aspect there is provided a clear ibuprofen composition that includes from about 15% to about 40% w/w of ibuprofen, from about 30% to about 70% w/w of polyethylene glycol, from about 1% to about 10% w/w of a metal carbonate, and from about 1% to about 10% w/w of water.

Embodiments of the composition may include one or more of the following features. For example, the ibuprofen may make up about 15% to about 30% w/w of the composition. The composition may be filled into soft gelatin capsules.

The polyethylene glycol may have an average molecular weight of about 300 to about 1000 and more particularly a molecular weight of about 400.

The composition may further include one or more active ingredients. The additional active ingredients may be one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan, chlorpheniramine, and pharmaceutically acceptable salts thereof.

In another general aspect there is provided soft gelatin capsules of ibuprofen providing enhanced dissolution and bioavailability of ibuprofen, the soft gelatin capsules comprising clear solutions of ibuprofen comprising:

a. from about 15% to about 40% w/w of ibuprofen,

b. from about 30% to about 70% w/w of polyethylene glycol,

c. from about 1% to about 10% w/w of a metal carbonate, and

d. from about 1% to about 10% w/w of water.

In another general aspect there is provided a process of preparing a clear ibuprofen composition. The process may include the steps of (a) dissolving one or more metal carbonates in water to form a solution, (b) adding ibuprofen and the solution of step (a) to polyethylene glycol, with optional heating, and (c) stirring to obtain a clear solution.

Embodiments of the composition may include one or more of the following features. For example, the ibuprofen may make up about 15% to about 30% w/w of the composition.

The polyethylene glycol may have an average molecular weight of about 300 to about 1000. In particular, the polyethylene glycol may have a molecular weight of about 400.

The process may further include one or more active ingredients. The additional active ingredients may be one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan, chlorpheniramine, and pharmaceutically acceptable salts thereof.

In another aspect there is provided a clear composition of ibuprofen and pseudoephedrine that includes from about 15% to about 40% w/w of ibuprofen, from about 3% to about 6% w/w of pseudoephedrine or a pharmaceutically acceptable salt thereof, from about 30% to about 70% w/w of polyethylene glycol, from about 1% to about 10% w/w of a metal carbonate, and from about 1% to about 10% w/w of water.

Embodiments of the composition may include one or more of the following features. For example, the ibuprofen may make up about 15% to about 30% w/w of the composition. The composition may be filled into soft gelatin capsules.

The polyethylene glycol may have an average molecular weight of about 300 to about 1000 and more particularly a molecular weight of about 400.

In another aspect there is provided a process of preparing a clear composition of ibuprofen and pseudoephedrine or a pharmaceutically acceptable salt thereof. The process may include the steps of (a) dissolving one or more metal carbonates in water to form a solution, (b) adding ibuprofen and the solution of step (a) to polyethylene glycol, with optional heating, (c) stirring to obtain a clear solution, and (d) adding pseudoephedrine or a pharmaceutically acceptable salt thereof and stirring to obtain a clear solution.

In another general aspect there is provided a method of relieving one or more of pain, tenderness, inflammation and stiffness caused by one or more of arthritis and gout and pains from one or more of the common cold, backache, and pain after surgery or dental work. The method includes administering a clear ibuprofen composition that can

include from about 15% to about 40% w/w of ibuprofen, from about 30% to about 70% w/w of polyethylene glycol, from about 1% to about 10% w/w of a metal carbonate, and from about 1% to about 10% w/w of water.

The method may include one or more of the following or the features described above. For example, the composition may further include one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine. The ibuprofen and the one or more active ingredients may be combined in a single pharmaceutical composition.

In another general aspect there is provided a clear ibuprofen composition that includes from about 15% to about 40% w/w of ibuprofen, from about 30% to about 65% w/w of polyethylene glycol, from about 1% to about 10% w/w of a metal carbonate, from about 1% to about 15% of a surfactant, and from about 1% to about 10% w/w of water.

Embodiments of the composition may include one or more of the following features. For example, the ibuprofen may make up about 15% to about 30% w/w of the composition. The composition may be filled into soft gelatin capsules.

The polyethylene glycol may have an average molecular weight of about 300 to about 1000 and more particularly a molecular weight of about 400.

The surfactant may be a non-ionic hydrophilic surfactant. The non-ionic hydrophilic surfactant may be one or more of polyoxyethylene alkylethers, polyethylene glycol fatty acids esters, polyethylene glycol glycerol fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, polyglyceryl fatty acid esters, polyoxyethylene glycerides, polyoxyethylene vegetable oils, and polyoxyethylene hydrogenated vegetable oils. In particular, the surfactant may be polyoxyethylene sorbitan fatty acid ester.

The composition may further include one or more active ingredients. The additional active ingredients may be one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

In another general aspect there is provided a process of preparing a clear ibuprofen composition. The process may include the steps of (a) dissolving one or more metal

carbonates in water to form a solution, (b) preparing a solution of one or more surfactants in polyethylene glycol with optional heating, (c) adding ibuprofen and the solution of step (a) to the solution of step (b), and (d) stirring to obtain a clear solution.

Embodiments of the process may include one or more of the following features. For example, the ibuprofen may make up about 15% to about 30% w/w of the composition.

The polyethylene glycol may have an average molecular weight of about 300 to about 1000. In particular, the polyethylene glycol may have a molecular weight of about 400.

The surfactant may be a non-ionic hydrophilic surfactant. The non-ionic hydrophilic surfactant may be one or more of polyoxyethylene alkylethers, polyethylene glycol fatty acids esters, polyethylene glycol glycerol fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, polyglyceryl fatty acid esters, polyoxyethylene glycerides, polyoxyethylene vegetable oils, and polyoxyethylene hydrogenated vegetable oils. In particular, the surfactant may be polyoxyethylene sorbitan fatty acid ester.

The process may further include one or more active ingredients. The additional active ingredients may be one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine.

In another aspect there is provided a clear composition of ibuprofen and pseudoephedrine that includes from about 15% to about 40% w/w of ibuprofen, from about 3% to about 6% w/w of pseudoephedrine or a pharmaceutically acceptable salt thereof, from about 30% to about 65% w/w of polyethylene glycol, from about 1% to about 10% w/w of a metal carbonate, from about 1% to about 15% of a surfactant, and from about 1% to about 10% w/w of water.

Embodiments of the composition may include one or more of the following features. For example, the ibuprofen may make up about 15% to about 30% w/w of the composition. The composition may be filled into soft gelatin capsules.

The polyethylene glycol may have an average molecular weight of about 300 to about 1000 and more particularly a molecular weight of about 400.

The surfactant may be a non-ionic hydrophilic surfactant. The non-ionic hydrophilic surfactant may be one or more of polyoxyethylene alkylethers, polyethylene glycol fatty acids esters, polyethylene glycol glycerol fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, polyglyceryl fatty acid esters, polyoxyethylene glycerides, polyoxyethylene vegetable oils, and polyoxyethylene hydrogenated vegetable oils. In particular, the surfactant may be polyoxyethylene sorbitan fatty acid ester.

In another aspect there is provided a process of preparing a clear composition containing ibuprofen and pseudoephedrine and pharmaceutically acceptable salts thereof. The process may include the steps of (a) dissolving one or more metal carbonates in water to form a solution, (b) preparing a solution of one or more surfactants in polyethylene glycol with optional heating, (c) adding ibuprofen and the solution of step (a) to the solution of step (b), (d) stirring to obtain a clear solution, and (e) adding pseudoephedrine or a pharmaceutically acceptable salt thereof, to the solution of step (d) with continuous stirring to obtain a clear solution.

In another general aspect there is provided a method of treatment of cough, cold, allergy, sinus and/or flu symptoms and the discomfort, pain, fever, and general malaise associated with it. The method includes administering a clear ibuprofen-pseudoephedrine composition that can include from about 15% to about 40% w/w of ibuprofen, from about 3% to about 6% w/w of pseudoephedrine or a pharmaceutically acceptable salt thereof, from about 30% to about 65% w/w of polyethylene glycol, from about 1% to about 10% w/w of a metal carbonate, from about 1% to about 15% of a surfactant, and from about 1% to about 10% w/w of water.

The method may include one or more of the following or the features described above. For example, the composition may further include one or more of glucosamine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine. The ibuprofen and the one or more active ingredients may be combined in a single pharmaceutical composition.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

Hydrophobic therapeutic agents, i.e., therapeutic compounds having poor solubility in aqueous solution, present problems in formulating such compounds for effective administration to patients. A well-designed formulation must be capable of presenting a therapeutically effective amount of the hydrophobic compound to the desired absorption site, in an absorbable form. Even this minimal functionality may be difficult to achieve when delivery of the hydrophobic therapeutic agent requires interaction with aqueous physiological environments, such as gastric fluids and intestinal fluids. Pharmaceutical compositions for delivery of such hydrophobic therapeutic agents must carry the hydrophobic compound through the aqueous environment while maintaining the hydrophobic compound in an absorbable form and avoiding the use of physiologically harmful solvents or excipients.

Soft gelatin capsules or softgels are predominantly used to contain liquids wherein the active ingredients are present in the dissolved or suspended state. Solutions also provide the best liquid form to obtain optimal "content uniformity" in softgel fill. In addition, a solution provides a faster and more uniform absorption of a pharmaceutical agent than a suspension. Because of these distinct technical advantages, solutions often are preferred over suspensions or other dispersions.

However, an appropriate solution of the pharmaceutical agent cannot always be achieved. Often, it is not possible to dissolve the pharmaceutical agent in a volume of solvent small enough to produce a softgel that is appropriate from the standpoint of economics and patient acceptance. Another constraint is the solvent itself. The solvent must have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a clear solution, and yet not hydrolyze, dissolve, or discolor the softgel capsule shell.

The present invention provides clear and stable solutions of ibuprofen and the process of preparing them.

The term 'clear solutions', as used herein, describes liquid pharmaceutical compositions, that are transparent and free from turbidity or cloudiness or any other foreign particulate matter.

The clear and stable solutions of ibuprofen generally include:

a. from about 15% to about 40% w/w of ibuprofen,
b. from about 30% to about 70% w/w of polyethylene glycol,
c. from about 1% to about 10% w/w of a metal carbonate, and
d. from about 1% to about 10% w/w of water.

Polyethylene glycols generally are clear, viscous liquids or white solids, which are soluble in water and many organic solvents. The polyethylene glycols useful herein are those which are liquids at room temperature or have a melting point slightly there above. Preferred polyethylene glycols are those having a molecular weight range from about 300 to about 1000. More preferred are the polyethylene glycols having a molecular weight range from about 400 to about 1000. Moreover, mixtures of two or more polyethylene glycols of different average molecular weight range can also be employed in the present invention. Polyethylene glycols may be present in amounts from about 30% to about 70% by weight.

The ibuprofen may be used in its free acid form. Ibuprofen may be present from about 15% to about 40% of the solution by weight.

Ibuprofen may be converted into its cationic salt by adding the metal carbonate as dry powder or as aqueous solution in polyethylene glycol, containing the active ingredient. Alternatively, ibuprofen and metal carbonate can also be added to polyethylene glycol. There may be partial or complete conversion of ibuprofen to its metal salt by the above mentioned process.

The term 'metal carbonate', as used herein, means carbonates and bicarbonates of any of the alkali and alkaline earth metals, for example sodium, lithium, calcium, magnesium, aluminium, and potassium. Examples of metal carbonates include sodium bicarbonate, calcium carbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, magnesium carbonate, magnesium bicarbonate, or mixtures thereof.

A surfactant may be also be added to the composition to assist in dissolution and/or dispersion of the ibuprofen after its release from the dosage form. Suitable surfactants can be ionic hydrophilic surfactants or non-ionic hydrophilic surfactants. The surfactant can be any surfactant suitable for use in pharmaceutical compositions. Suitable hydrophilic surfactants may be anionic, cationic, zwitterionic or non-ionic; particularly non-ionic hydrophilic surfactants. Suitable non-ionic hydrophilic surfactants include one or more of polyoxyethylene alkylethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member selected front the group consisting of fatty acids, glycerides, vegetable oil hydrogenated vegetable oils, and sterols; and mixtures thereof.

In particular, polyoxyethylene sorbitan fatty acid esters are employed. Suitable examples of these are polyethylene glycol-20 laurate, polyethylene glycol-20 oleate, polyethylene glycol-35 castor oil (commonly known as Cremophor® EL), polyethylene glycol-40 palm kernel oil, polyethylene glycol-40 hydrogenated castor oil, polyethylene glycol-60 corn oil (commonly known as Labrafil®), polyethylene glycol-25 glyceryl trioleate, polyglyceryl-10 laurate, polyethylene glycol-6 caprate/caprylate glycerides, polyethylene glycol-8 caprate/caprylate glycerides (commonly known as Labrasol®), polyethylene glycol-30 cholesterol, polysorbate 20, polysorbate 80 (commonly known as Tween® 80), polyoxyethylene-9 lauryl ether, polyoxyethylene-23 lauryl ether, polyoxyethylene-10 oleyl ether, polyethylene glycol-24 cholesterol, sucrose monostearate, sucrose monolaurate and poloxamers. The surfactants may be present from about 1 to about 15%, by weight of the formulation.

The term 'pharmaceutical composition', as used herein, relates to soft gelatin capsule fill material or solution with the active ingredient ready to be filled into soft gelatin capsule.

The pH of the composition before filling into the softgel may be in the range from about 2.5 to about 7.5. The temperature during the processing may be in the range from about 25°C to about 65°C to carry out the conversion of ibuprofen into its metal salt form.

The small amount of water present acts to form a salvation sphere around the acid salt permitting it to go into solution in the polyethylene glycol. Water may be present in amounts ranging from about 1% to about 10% by weight of the solution.

Additional ingredients which enhance the solubility of the active pharmaceutical ingredient in polyethylene glycol can be used as well; provided such ingredients are present only in amounts sufficient to preserve the desired viscosity and that do not degrade the gelatin capsule. Examples of additional ingredients include, but are not limited to, glycerin, propylene glycol, and polyvinylpyrrolidone, and combinations thereof. The amount and combination of additional ingredient(s) used may vary according to the chemical properties of the other ingredients used in the process.

Conventional additives can also be used in conjunction with the process of the invention as well, including but not limited to, preservatives, stabilizers, wetting agents, coloring agents, and the like.

A process of preparing the pharmaceutical composition includes the steps of:

(a) dissolving metal carbonate in water to form a solution,

(b) adding ibuprofen and the solution of step (a) to polyethylene glycol with optional heating, and

(c) stirring to obtain a clear solution.

The clear solution may be encapsulated into one-piece gelatin sheath or shell that includes a plasticizer.

The softgel capsules may be produced in a known manner with a rotary die process in which a molten mass of a gelatin sheath formulation is fed from a reservoir onto drums to form two spaced sheets or ribbons of gelatin in a semi-molten state. These ribbons are fed around rollers and brought together at a convergent angle into the nip of a pair of roller dies that include opposed die cavities. A fill formulation to be encapsulated is fed into the wedge-shaped jointer of the ribbons.

The gelatin ribbons are continuously conveyed between the dies, with portions of the fill formulation being trapped between the sheets inside the die cavities. The sheets are then pressed together, and severed around each die so that opposed edges of the sheets

flow together to form a continuous gelatin sheath around the entrapped medicament. The part of the gelatin sheet that is severed from the segments forming the capsules is then collected for recycling, and the soft capsules are dried.

Various sheath formulations known in the prior art may be used to encapsulate the fill formulations of the present invention. For example, suitable sheath formulations may include from about 35 to about 50% by weight of gelatin; at least 20% by weight, and in particular, up to about 40% by weight of a plasticizer; and from about 25 to about 50% by weight of water. These formulations, when formed into capsules and dried, may result in capsule sheaths that includes from about 45 to about 75% by weight of gelatin; from about 20% to about 40% by weight of plasticizer; and from about 5% to about 15% by weight of water.

Without being limited by theory, the water is believed to aid in the rapid dissolution or rupture of the soft gelatin shell upon contact with the gastrointestinal fluids encountered in the body. The ratio of gelatin to water may vary from 1:0.75 to 1:0.92. The amount of plasticizer added to the sheath is the determining factor as to how hard or soft the resulting capsule shell will be. In particular, the ratio of gelatin to plasticizer may vary from 1:0.35 to 1: 0.48.

The gelatin will normally have a bloom in the range of from about 150 to about 275, and may be Type A or B gelatins, or a mixture thereof. Limed bone, acid bone, fish and/or pig skin gelatins may be used.

The susceptibility of gelatin to chemical modification is well known. Of the variety of reagents capable of interacting covalently with gelatin, formaldehyde has been studied most extensively. Cross linking of gelatin with formaldehyde has been used to produce enteric hard and soft capsules. However, when gelatin capsules intended for immediate release of their contents are exposed to trace levels of formaldehyde, the effect on in vitro dissolution rates may be adverse. Modification of the soft gelatin capsule shell is therefore necessary in order to avoid such problems. In order to provide adequate flexibility and strength to the shell, various plasticizers have been probed. Examples of suitable plasticizers include glycerin, xylitol, sorbitol, polyglycyerol, non-crystallizing solutions of sorbitol, glucose, fructose and glucose syrups with varying equivalents. A commercial plasticizer is ANDRISORB (supplied by Roquette, France), which is a

proprietary mixture of sorbitol, sorbitans, maltitol and mannitol. While glycerin can be used as a plasticizer, it has been found that the ibuprofen may be esterified with the glycerin, thus reducing the amount of available free form of the ibuprofen. Therefore, the non-glycerin plasticizers are preferred.

The sheath formulations may also contain other ingredients, such as taste modifiers, coloring agents, and moisture retaining agents. Taste modifiers include non-reducing sugars, such as xylitol, maltitol, or Lycasin™ manufactured by Roquette America, Inc. and normally may be present up to about 5% by weight of the sheath composition. Suitable moisture retaining agents include celluloses, cellulose derivatives, starches, starch derivatives, vegetable gums, non-hygroscopic, mono-, di- and oligosaccharides, and silicon dioxide. Various FD&C coloring agents may be used to impart the desired color to the capsule.

Compositions of the invention are useful in relieving the pain, tenderness, inflammation (swelling) and stiffness caused by arthritis and gout. It may also be used to reduce fever and to relieve headaches, muscle aches, menstrual pain, aches and pains from the common cold, backache, and pain after surgery or dental work.

The pharmaceutical composition may further include one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, hydrocodone, COX-2 inhibitors, alprazolam, dextromethorphan and chlorpheniramine. The ibuprofen and the one or more active ingredients may be combined in a single pharmaceutical composition, such as a soft gelatin capsule or softgel. Administering the present invention which further contains pseudoephedrine may treat common cold and flu-like illnesses. Pseudoephedrine and its pharmaceutically acceptable salts are well recognized by those skilled in the art as safe and effective nasal decongestants. In particular, the widely used salts are the hydrochloride and the sulfate. Pharmacologically, pseudoephedrine is a sympathomimetic amine and is used as a bronchodilator and as a peripheral vasoconstrictor. It is indicated for temporary relief of nasal congestion due to the common cold and for temporary relief of nasal congestion associated with sinusitis. Pseudoephedrine may constitute from about 3% to about 6% w/w of the total composition.

The following examples illustrate various aspects of the present inventions. These examples are for illustration only and do not limit the scope of the inventions.

Example 1:

Soft gelatin capsule gel mass composition

S.No.	Ingredients	Quantity (% w/w)
1.	Gelatin	46.28
2.	Purified water	37.0
3.	Sorbitol Special Solution / ANDRISORB	16.5
4.	Color	0.005
5.	Methyl paraben	0.2
6.	Propyl paraben	0.02

Composition to be incorporated in the soft gelatin capsule

S. No	Ingredients	Percent w/w
1.	Ibuprofen	32.2
2.	Polyethylene glycol	59.0
3.	Potassium carbonate	4.4
4.	Purified water	4.4

Process:

1. Polyethylene glycol was stirred with optional heating at a temperature of up to 45^0C.
2. Potassium carbonate was dissolved in purified water.
3. Ibuprofen and potassium carbonate solution were added alternately to the polyethylene glycol with optional heating under constant stirring at a temperature of up to 45^0C.
4. Stirring was continued till a clear solution was obtained.
5. The clear solution of step 4 was filled in soft gelatin capsules.

Example 2:

Soft gelatin capsule gel mass composition

Similar to that of Example 1

Composition to be incorporated in the soft gelatin capsule

S. No	Ingredients	Percent w/w
1.	Ibuprofen	31.0
2.	Pseudoephedrine hydrochloride	4.6
3.	Polyethylene glycol 400	56.0
4.	Potassium carbonate	4.2
5.	Purified water	4.2

Process:

1. Polyethylene glycol was stirred with optional heating at a temperature of up to 45^{0}C.
2. Potassium carbonate was dissolved in purified water.
3. Ibuprofen and potassium carbonate solution were added alternately to the polyethylene glycol with optional heating under constant stirring at a temperature up to 45°C.
4. Stirring was continued till a clear solution was obtained.
5. Pseudoephedrine hydrochloride was added and stirring was continued till a clear solution was obtained.
6. The clear solution of step 4 was filled in soft gelatin capsules.

Example 3:

Soft gelatin capsule gel mass composition

Similar to that of Example 1

Composition to be incorporated in the soft gelatin capsule

S. No	Ingredients	Percent w/w
1.	Ibuprofen	32.2
2.	Polyethylene glycol	52
3.	Potassium carbonate	4.4
4.	Cremophor® EL	7.0
5.	Purified water	4.4

Process:

1. Polyethylene glycol was stirred with optional heating at a temperature of about 45^0C to 60°C and Cremophor® EL was dissolved in it with stirring.
2. Potassium carbonate was dissolved in purified water.
3. Ibuprofen and potassium carbonate solution were added alternately to the surfactant-polyethylene glycol solution with constant stirring at a temperature of about 45^0C to 60°C.
4. Stirring was continued at a temperature of about 45-60°C for about 30-45 minutes till a clear solution was obtained.
5. The clear solution of step 4 was allowed to cool to room temperature and filled in soft gelatin capsules.

Example 4:

Soft gelatin capsule gel mass composition

Similar to that of Example 1

Composition to be incorporated in the soft gelatin capsule

S. No	Ingredients	Percent w/w
1.	Ibuprofen	30.77
2.	Pseudoephedrine hydrochloride	4.62
3.	Polyethylene glycol 400	44.61
4.	Cremophore® EL	11.7
5.	Potassium carbonate	4.15
6.	Purified water	4.15

Process:

1. Polyethylene glycol was stirred with optional heating at a temperature of about 45^0C to 60°C and Cremophor® EL was dissolved in it with stirring.
2. Potassium carbonate was dissolved in purified water.
3. Ibuprofen and potassium carbonate solution were added alternately to the surfactant-polyethylene glycol solution with constant stirring at a temperature of about 45°C to 60°C.

4. Stirring was continued at a temperature of about 45-60°C for about 30-45 minutes till a clear solution was obtained.
5. Pseudoephedrine hydrochloride was added and stirring was continued till a clear solution was obtained.
6. The clear solution of step 5 was allowed to cool to room temperature and filled in soft gelatin capsules.

Example 5:

Soft gelatin capsule gel mass composition

Similar to that of Example 1

Composition to be incorporated in the soft gelatin capsule

S. No	Ingredients	Percent w/w
1.	Ibuprofen	32.2
2.	Pseudoephedrine hydrochloride	4.85
3.	Polyethylene glycol 400	51.0
4.	Labrasol®	3.25
5.	Potassium carbonate	4.35
6.	Purified water	4.35

Process:

1. Polyethylene glycol was stirred with optional heating at a temperature of about 45^{0}C to 60°C and Labrasol® was dissolved in it with stirring.
2. Potassium carbonate was dissolved in purified water.
3. Ibuprofen and potassium carbonate solution were added alternately to the labrasol-polyethylene glycol solution with constant stirring at a temperature of about 45^{0}C to 60°C.
4. Stirring was continued at a temperature of about 45-60°C for about 30-45 minutes till a clear solution was obtained.
5. Pseudoephedrine hydrochloride was added and stirring was continued till a clear solution was obtained.

6. The clear solution of step 5 was allowed to cool to room temperature and filled in soft gelatin capsules.

Pharmacokinetics:

The soft gelatin capsules prepared according to Example 4 were subjected to pharmacokinetic studies in comparison with Advil Cold and Sinus capsules, currently marketed by Wyeth, in normal healthy subjects under fasting conditions.

Values for pharmacokinetic parameters, including observed C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$, were calculated using standard non-compartmental methods. The results as indicated by ratio of test to reference are shown in Table 1.

Test (A): Soft gelatin capsules prepared as per Example 4

Reference (R): Advil Cold and Sinus capsules (Wyeth)

Table 1: Summary of pharmacokinetic parameters

		Parameters		
		Cmax (ng/ml)	**AUC $_{(0\text{-}t)}$ (ng.hr /ml)**	**AUC $_{(0\text{-}\infty)}$ (ng.hr /ml)**
Ibuprofen	Ratio % (A/R)	107.17	97.51	96.59
	90% Confidence intervals	92.99-123.51	86.88-109.44	86.10-108.35
Pseudoephedrine hydrochloride	Ratio % (A/R)	106.55	97.53	100.05
	90% Confidence intervals	96.34-117.86	85.06-111.84	89.44-111.92

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.